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Anemia types in hypothyroid patients in a Coimbatore tertiary care hospital: A prospective observational study

Priyanka Sasidharan [1], Yoganathan Chidambaram [2], Bhargavi Kumar [2], Petchiappan Velammal [2], Sujith Kumar [2]

[1]Department of General Medicine, Government Medical College Nizamabad, Telangana, India;
[2]Department of General Medicine, PSG IMS & R, Coimbatore, India
E-mail: yoganathancc@gmail.com

Objective. Hypothyroidism is a syndrome characterized by clinical manifestations associated with thyroid hormone deficiency. The thyroid hormone plays a pivotal role in the hematopoietic system and stimulates precursors of erythropoietin gene expression. Therefore, anemia is a common clinical manifestation in hypothyroid individuals. The goal of this study was to carry out a prospective analysis of the prevalence of anemia, its types, and the etiology behind the differing anemia morphology among hypothyroid patients.

Methods. The study was conducted with a sample size of 100 patients suffering from hypothyroidism. The methodology of the study included a questionnaire and consent filling for general information followed by a complete blood test for assessment of blood count, peripheral smear, FT3/FT4 (free triiodothyronine/thyroxine), anemia profile, vitamin B12, folate, LDH (lactate dehydrogenase), reticulocyte count, and thyroid stimulating hormone (TSH).

Results. The results of the study are in line with the previous studies and showed severe anemia and prevalence among women of reproductive age. Microcyte hypochromic anemia was found to be the most common type of morphological anemia, which was validated with low hemoglobin (Hb) levels, vitamin B12, FT3, and FT4. Additionally, TSH showed a positive correlation with reticulocyte count, LDH, and Hb in Pearson's correlation test.

Conclusion. The study summarizes the need to investigate the underlying etiological agent responsible for better therapy and management of hypothyroidism and anemia suggesting also the use of oral iron supplements along with levothyroxine therapy.

Key words: anemia, hypothyroidism, iron deficiency, TSH, microcyte hypochromic anemia

Thyroid hormone plays a pivotal role in the functioning and maintenance of human metabolism. Hypothyroidism is a syndrome characterized by clinical manifestations associated with thyroid hormone deficiency. There is an overall slowing of all physiological processes in hypothyroidism including the hematopoietic system (Bashir et al. 2012). The thyroid plays a crucial role in erythropoiesis exerting a stimulating effect to proliferate erythrocyte precursors and erythropoietin gene expression, and erythropoietin production in kidneys. Etiopathogenesis of anemia in hypothyroidism can be related to low bone marrow stimulation, low erythropoietin production, nutrition deficiency, and other co-morbid conditions (pregnancy, celiac diseases, autoimmune hemolytic anemia, chronic kidney disease, soft tissue rheumatic disorders, aplastic anemia) (Szczepanek-Parulska et al. 2017). Normal thyroid status is also dependent on trace elements, like iron, selenium, and zinc, for synthesis and

Corresponding author: Dr. Yoganathan Chidambaram, Assistant professor, Department of General Medicine, PSG IMS & R, Coimbatore, India; 14, Sakthi Vinayaka Nagar, Vilankurichi, Coimbatore, Tamilnadu, India 641035; phone: 00919942460735; e-mail: yoganathancc@gmail.com.

metabolism. In the meanwhile, studies have shown a correlation between iron deficiency and the thyroid dysfunction (Soliman et al. 2017). Around 20–60% of patients with hypothyroidism have been associated with anemia. Anemia means decreased level of red blood cells (RBC) or hemoglobin in the blood. Anemia associated with thyroid diseases is often underestimated. From several types of anemia that may occur in the course of thyroid malfunctioning, normocytic anemia is the most common, and microcytic and macrocytic ones are less prevalent (Das et al. 2012). Over 90% of the individuals are affected with anemia, out of which 50% are due to iron deficiency and the remaining due to vitamin A, B12, folate deficiency, malaria, HIV, infections, sickle cell, and other congenital disorders (Ahmed and Mohammed 2020). In the developing countries (India), non-communicable diseases like hypothyroidism and its underlying diseases are often neglected. Around 42 million people suffer from thyroid diseases. In women, the prevalence is double in comparison with men causing depression and fatigue affecting the quality of life and productivity (Islam et al. 2021). Considering the current state of the disease, we conducted a prospective observational study on the prevalence of anemia, its types, and the etiology behind the differing morphology of anemia among hypothyroid patients.

Material and Methods

Patients and methods. Before starting the study, a proposal was approved by the institutional ethics committee (Ref. #17/404). Thereafter, 100 consecutive patients with symptoms suggestive of hypothyroidism visiting the General Medicine O/I Patient (out/in patients) Department of a tertiary care hospital at Coimbatore, Tamil Nadu, were selected for the study based on the inclusion and exclusion criteria, following which the patients were divided into two subgroups: overt and subclinical. Their hypothyroid status was first assessed by means of a questionnaire (Glynn and Drake 2018; Jameson et al. 2018). The questionnaire explained in the vernacular language considered the general symptoms of anemia and hypothyroidism such as fatigue, constipation, unexplained weight gain, decreased sweating, depression, pallor, breathlessness, palpitations, and irregular menstrual cycles. Moreover, informed consent was obtained from the volunteering participant's values assessed for these patients by a blood test. Patients with elevated thyroid stimulating hormone (TSH) in the blood were selected for the study (Wildisen et al. 2021). Assessment of complete count, peripheral smear, free triiodothyronine (FT3)/thyroxine (FT4), anemia profile, fasting B12, folate levels, lactate dehydrogenase (LDH), and reticulocyte count, were also performed. Hemoglobin (Hb), RBC and white blood cells (WBC) were determined by DxH 900 hematology analyzer (Beckman Coulter). TSH, FT3, FT4, ferritin, vitamin B12 and folate were measured by Cobas 6000 analyzer (Roche Diagnostics). Serum iron and unsaturated iron-binding capacity (UIBC) were measured by Cobas c 501 module (Roche Diagnostics).

Statistical analysis. A descriptive Pearson statistical correlation interpretation corresponding to age, gender, and hematological parameters was also performed using the SPSS software package (version 16.0, Chicago, IL, USA) where two tailed p values <0.05 were considered as significant.

Results

Demographic measures of mean age, gender distribution, and frequency of anemia among hypothyroid patients. The clinical data of the patients in subclinical and overt hypothyroid groups are presented in Table 1. There are significant differences in mean age, Hb levels, packed cell volume (PCV) levels, RBC count, TSH, FT3, and FT4 levels between the overt and subclinical groups (Table 1); patients in the subclinical group were found to be more anemic than patients in the overt group. In overt and subclinical groups, the highest number of patients with anemia was in the age category of 40–59 years, 30 and 12 patients, respectively. The lowest number of cases with anemia was in the age category 18–20 years (Figure 1). Only 23 men of the 100 patients had hypothyroidism, out of which 5 men had subclinical hypothyroidism and 18 men had overt hypothyroidism. Globally, the frequency of anemia between hypothyroid patients in the overt group was 72% and in subclinical group 28% with no statistical difference in frequency ($p=0.316$) (Figure 1).

Most of hypothyroid patients had moderate (Hb 8–10.9 g/dL) or severe (Hb count <8 g/dL) anemia (Table 2), and women were the most affected (Figure 2).

In case of severity, the biochemical levels of mean Hb, PCV, RBC count, red cell distribution width (RDW), mean corpuscular hemoglobin concentration (MCHC), and ferritin showed statistical differences between the different degrees of anemia – mild, moderate and severe (Table 2).

Table 1
Clinical and laboratory data of patients in subclinical and overt hypothyroid groups

Parameter	Reference range		Overt		Subclinical		Total		p value
	Male	Female	Mean±SD	N	Mean±SD	N	Mean±SD	N	
Age (years)			53.86±16.44	72	43.32±17.39	28	50.91±17.29	100	0.006**
Hb (g/dL)	13.0–16.5	12.0–16.0	8.28±1.98	72	7.16±2.76	28	7.97±2.27	100	0.026*
PCV (%)	40–49	35–48	26.47±5.75	72	22.73±8.27	28	25.42±6.73	100	0.012*
MCV (fl)	80–100	80–100	80.35±19.17	72	86.87±22.82	28	82.18±20.36	100	0.151
MCH			25.30±7.07	72	27.45±8.31	28	25.90±7.46	100	0.195
MCHC (g/dL)	32–35	32–35	31.18±1.76	72	31.27±1.93	28	31.20±1.80	100	0.826
RBC ($x10^6$/µL)	4.6–6.0	4.0–5.4	3.43±0.87	72	2.77±1.11	28	3.25±0.98	100	0.002**
WBC ($x10^3$/µL)	4–11	4–11	8.33±4.84	72	7.27±5.26	28	8.03±4.96	100	0.339
Platelets ($x10^3$/µL)	150–450	150-450	275.31±146.22	72	192.96±123.44	28	252.25±144.46	100	0.010*
RDW (%)	10–15	10–15	20.10±5.81	72	20.63±7.08	28	20.25±6.16	100	0.705
TSH (micro IU/ml)	0.24–4.20	0.24–4.20	18.99±29.20	72	7.08±2.24	28	15.65±25.34	100	0.034*
FT3 (pg/ml)	2.0–4.4	2.0–4.4	2.11±0.72	26	2.72±0.50	8	2.26±0.72	34	0.034*
FT4 (ng/dL)	0.932–1.710	0.932-1.710	1.04±0.33	72	1.20±0.24	28	1.08±0.31	100	0.023*
Serum iron (mcg/dL)	59–158	37–145	40.85±47.27	60	54.29±62.12	21	44.33±51.46	81	0.306
Ferritin (ng/mL)	30–400	13–150	321.81±529.38	59	137.38±159.29	21	273.40±467.81	80	0.121
TIBC (mcg/dL)	251–406	251–406	318.53±100.92	57	304.10±82.92	20	314.78±96.25	77	0.568
UIBC (mcg/dL)	112–346	112–346	276.09±120.70	57	251.45±128.37	20	269.69±122.37	77	0.442
Vitamin B12 (pg/mL)	199–663	199–663	499.95±546.13	37	253.29±276.58	21	410.64±479.08	58	0.059
Folic acid (ng/mL)	4.6–34.8	4.6–34.8	13.40±10.91	34	9.63±9.95	20	12.00±10.63	54	0.212

Abbreviations: FT3 – free triiodothyronine; FT4 – free thyroxine; Hb – hemoglobin; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; MCV – mean corpuscular volume; PCV – packed cell volume; RBC – red blood cell count; RDW – red cell distribution width; SD – standard deviation; TIBC – total iron-binding capacity; TSH – thyroid stimulating hormone; UIBC – unsaturated iron-binding capacity; WBC – white blood cells. *Significant at 5% level of significance; ** Significant at 1% level of significance.

Classification of types of anemia among subclinical and overt hypothyroid patients based on mean corpuscular volume (MCV), MCHC, and peripheral smear pictures. Based on the MCV, the anemia was classified as microcytic, normocytic, and macrocytic, whereas most of the patients in overt and subclinical groups was presented by the microcytic hypochromic type of anemia (Figure 3). Based on the MCHC, the anemia was classified as hypochromic and normochromic, most of the patients in overt and subclinical groups was presented by hypochromic anemia type (Figure 4). Based on the peripheral smear pictures, anemia was classified as dimorphic, macrocytic normochromic, macrocytic hypochromic, macrocytic hyperchromic, microcytic hypochromic, normocytic hypochromic, and normocytic normochromic. In this case, most of the patients of both overt and subclinical groups were microcytic hypochromic (Figure 5).

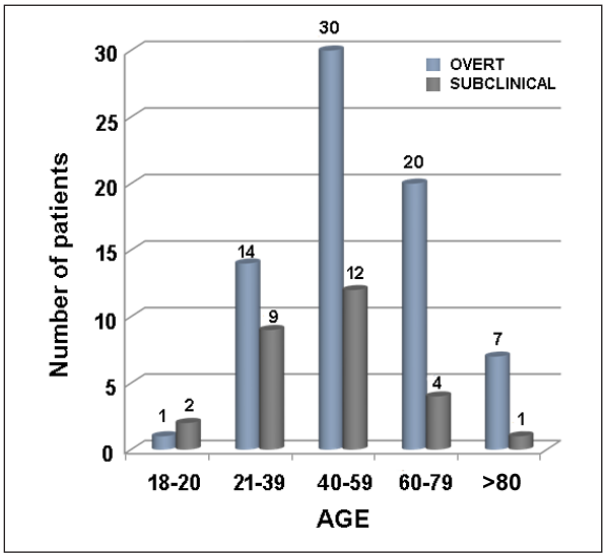

Figure 1. The age distribution of anemia among subclinical and overt hypothyroid patients.

Table 2
Demographic and biochemical parameters anemia severity among subclinical and overt hypothyroid patients

Anemia	Reference range		Mild (11-19)		Moderate (8.0–10.9)		Severe (<8)		Total		p-value
	Male	Female	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	
Age (years)			48.50±14.81	8	50.00±16.79	43	51.94±18.45	48	50.82±17.35	99	0.81
Hb (g/dL)	13.0–16.5	12.0-16.0	11.54±0.38	8	9.45±0.74	43	5.96±1.31	48	7.93±2.24	99	0.00**
PCV (%)	40–49	35–48	35.68±1.53	8	29.67±2.39	43	19.66±4.32	48	25.30±6.66	99	0.00**
MCV (fl)	80–100	80–100	92.44±12.34	8	82.51±14.54	43	79.78±25.11	48	81.99±20.38	99	0.26
MCH			29.96±4.17	8	26.39±5.28	43	24.64±9.16	48	25.83±7.46	99	0.14
MCHC (g/dL)	32–35	32–35	32.38±0.84	8	31.86±1.22	43	30.39±2.00	48	31.19±1.80	99	0.00**
RBC ($\times 10^6/\mu L$)	4.6–6.0	4.0–5.4	3.92±0.54	8	3.70±0.68	43	2.72±1.01	48	3.24±0.99	99	0.00**
WBC ($\times 10^3/\mu L$)	4–11	4–11	7.64±2.85	8	8.50±5.23	43	7.65±5.06	48	8.02±4.98	99	0.70
Platelets ($\times 10^3/\mu L$)	150–450	150–450	253.38±95.69	8	253.84±140.25	43	250.50±158.14	48	252.18±145.19	99	0.99
RDW (%)	10–15	10–15	15.51±1.19	8	18.27±4.70	43	22.88±6.74	48	20.28±6.18	99	0.00**
TSH (micro IU/ml)	0.24–4.20	0.24–4.20	18.19±33.91	8	14.02±25.06	43	16.84±24.77	48	15.72±25.46	99	0.84
FT3 (pg/ml)	2.0–4.4	2.0–4.4	1.99±1.14	3	2.32±0.79	13	2.25±0.62	18	2.26±0.72	34	0.78
FT4 (ng/dL)	0.932–1.710	0.932–1.710	1.01±0.46	8	1.12±0.30	43	1.07±0.30	48	1.09±0.31	99	0.57
Serum iron (mcg/dL)	59–158	37–145	74.00±18.38	2	40.44±24.80	36	46.21±66.82	43	44.33±51.46	81	0.64
Ferritin (ng/mL)	30–400	13–150	45.50±13.44	2	443.78±611.56	36	138.21±235.90	42	273.40±467.81	80	0.01*
TIBC (mcg/dL)	251–406	251–406	329.00	1	293.63±76.36	35	332.49±109.21	41	314.78±96.25	77	0.21
UIBC (mcg/dL)	112–346	112–346	268.00	1	252.43±91.88	35	284.46±144.18	41	269.69122.37	77	0.53
Vitamin B12 (pg/mL)	199–663	199–663	289.50±232.66	8	456.56±370.01	18	423.90±581.47	31	415.35±481.98	57	0.72
Folic acid (ng/mL)	4.6–34.8	4.6–34.8	10.88±13.30	7	16.03±13.76	15	10.45±8.02	31	12.09±10.71	53	0.25
LDH	135–225	135–225			749.88±1085.89	9	899.42±1310.37	19	851.36±1224.40	28	0.77

Abbreviations: FT3 – free triiodothyronine; FT4 – free thyroxine; Hb – hemoglobin; LDH – lactate dehydrogenase; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; MCV – mean corpuscular volume; PCV – packed cell volume; RBC – red blood cell count; RDW – red cell distribution width; SD – standard deviation; TIBC – total iron-binding capacity; TSH – thyroid stimulating hormone; UIBC – unsaturated iron-binding capacity; WBC – white blood cells. *Significant at 5% level of significance; ** significant at 1% level of significance.

Prevalence of various deficiencies. Most deficiencies have contributed to anemia in hypothyroid patients. Iron and vitamin B12 deficiency affected anemia in the overt hypothyroid patients, while the patients in subclinical group were severely affected due to folate and vitamin B12 deficiency (Table 3).

Mean TSH values among the various types of anemia among subclinical and overt hypothyroid patients. TSH levels were the highest in patients with mild anemia followed by patients with severe and moderate anemia (Figure 6, Table 2). Pearson correlation among the various hematological parameters revealed a positive correlation between LDH and MCV (p=0.654), LDH and TSH (p=0.054), TSH and reticulocyte count (p=0.069). On other hand, Hb positively correlated with TSH (p=0.010), but negatively with LDH (p=0.164) and reticulocyte count (p=0.131).

Discussion

Anemia is the most common condition affecting 27% of individuals worldwide. The lack of healthy erythrocytes and reduced circulation of erythrocytes causes anemia. Hemoglobin levels of <13 g/dl in men and <12 g/dl in women are considered as anemic

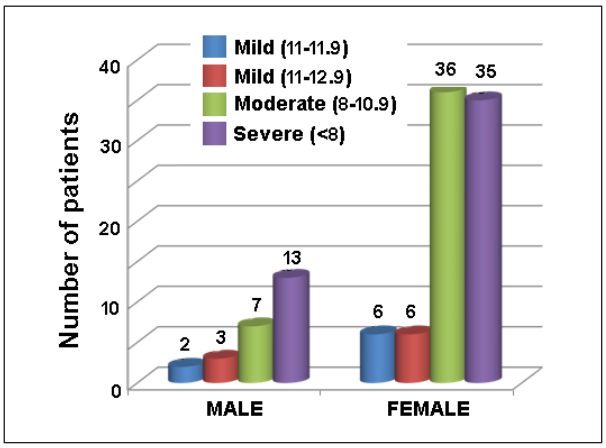

Figure 2. The frequency of anemia severity among male and female hypothyroid patients.

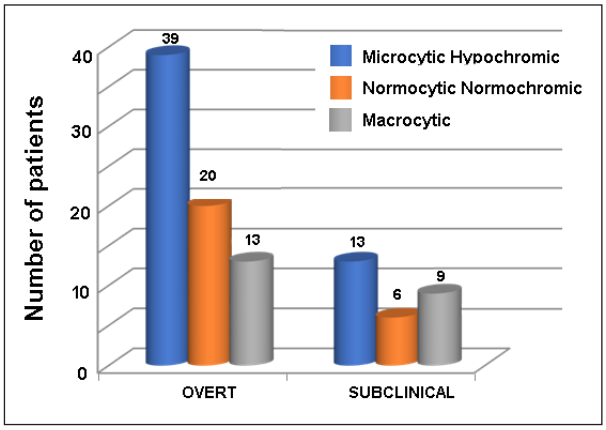

Figure 3. Various types of anemia among subclinical and overt hypothyroid patients based on mean corpuscular volume (MCV).

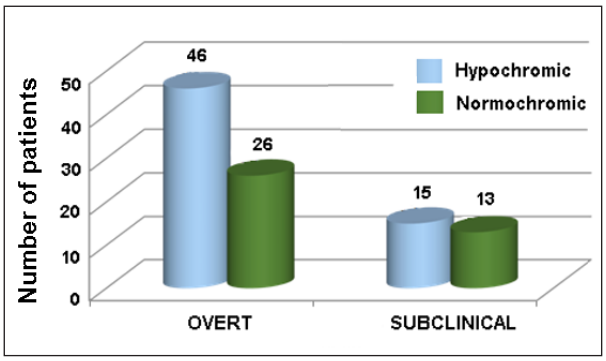

Figure 4. Various types of anemia among subclinical and overt hypothyroid patients based on mean corpuscular hemoglobin concentration (MCHC).

(Kassebaum et al. 2016). The thyroid gland plays a crucial role in hematopoiesis and therefore, it is associated with blood disorders on malfunctioning.

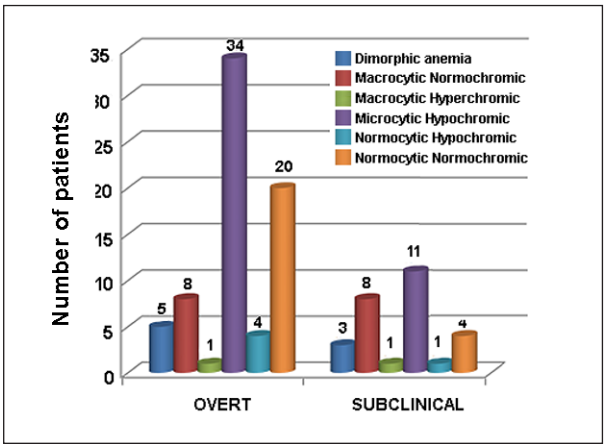

Figure 5. Peripheral smear picture among subclinical and overt hypothyroid patients.

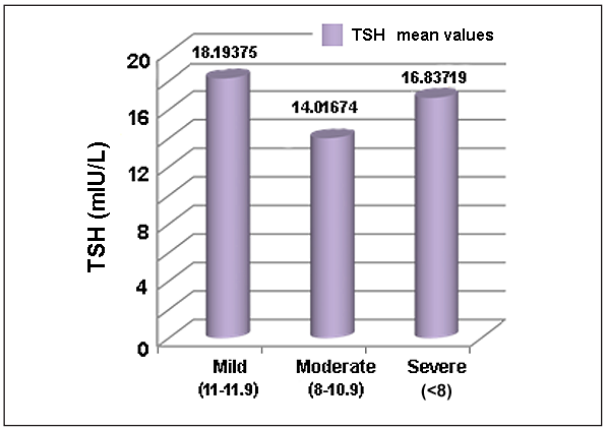

Figure 6. Thyroid stimulating hormone (TSH) values in various types of anemia among subclinical and overt hypothyroid patients.

The subclinical thyroid group of patients is clinically manifested with faulty TSH and normal thyroid functioning, whereas the overt group represents a suppressed functioning of the thyroid gland in producing T4 follicles and elevated TSH (Gavrila 2012). While subclinical thyroid is mild in nature, overt hypothyroidism is severe and treated with levothyroxine. In our study, the most affected individuals were in the overt group and very few in the subclinical group. Correspondingly, in a study among European participants with a mean age of 56.77 years, about 54.2% were women who reported anemia. From them, 4.9% of participants reported hypothyroidism concluding hypothyroidism to be associated with a high risk of anemia (van Vliet et al. 2022). Another case-controlled study has also shown a female predominance in patients with thyroid dysfunction with the peak age at the forties,

Table 3
Prevalence of various deficiencies

S. No.	Condition	Count		Count Total	Deficiency (%)		Total (%)
		Overt	Subclinical		Overt	Subclinical	
a.	Iron	16	2	18	88.9	11.1	100
b.	Vitamin B12	5	5	10	50.0	50.0	100
c.	Folate	1	2	3	33.3	66.7	100
d.	Serum iron + vitamin B12	4	5	9	44.4	55.6	100
e.	Iron + folate	1	4	5	20.0	80.0	100
f.	Vitamin B12 + folate	2	4	6	33.3	66.7	100
g.	Serum iron + B12 + folate	1	1	2	50.0	50.0	100
h.	Chronic disease	22	10	32	68.8	31.2	100

and demonstrated that thyroid dysfunction affected all blood parameters except platelets (Ahmed and Mohammed 2020). While most patients were initially affected with mild subclinical hypothyroidism, they gradually progress to clinical overt hypothyroidism along with comorbidities like diabetes mellitus, cardiovascular disorder and pernicious anemia (Wildisen et al. 2021). Some reports of meta-analysis data of cohorts also ascertain that the prevalence of anemia is associated mostly with hypothyroidism (Wopereis et al. 2018).

In considering the anemia class, the current study showed microcytic hypochromic as the most prevalent class of anemia seen in both overt and subclinical groups. Therefore, it demonstrates the smaller size, pale color RBC due to low hemoglobination and low MCV accompanied with iron deficiency. Likewise, a study of Akbarpour et al. (2022) has previously reported that microcytic hypochromic anemia is related to poor nutrition (deficiency in folic acid, iron and vitamin B12), thalassemia and other chronic diseases mostly seen in developing countries. Another study done on migrant refugee cohort has reported microcytic hypochromic anemia as the second highest subtype, with iron deficiency increasing with age and nutrition (Jablonka et al. 2018).

Even in cases of severity where the Hb levels are <8 g/dL, women are the most affected subjects. In our study, severe groups showed low levels of Hb, PCV, RBC count, RDW, MCH concentration, and ferritin in the overt and subclinical groups. Data are corresponding with notion that severe and chronic anemia is mainly caused due to iron deficiency (Khatiwada et al. 2016). In the developing countries like India, women and children <5 years are mostly affected due to the heavy blood loss during menstruation, childbirth, and malnutrition. The nutritional deficiencies and lack of absorption from the diet also become a primary cause of anemia. Likewise, a study of Islam and co-workers (2021) has brought out the correlation between essential micronutrient iron and anemia among hypothyroid patients. Iron deficient anemia impairs thyroid production in humans and animals. In our study, prevalence of anemia due to other deficiencies like iron, vitamin B12, folate, serum iron, and chronic diseases were also observed (Khatiwada et al. 2016). Similarly, studies reported by Soliman et al. (2017) also have accounted for lowered vitamin B12, folate, and iron deficiency in primary hypothyroid patients.

TSH is an important hormone for the metabolic stimulation of the thyroid gland. In our study, TSH showed a positive correlation with LDH, Hb, and reticulocyte count, which was similar to a cohort study performed by Bremner and co-workers (2012). Similarly, Montagnana et al. (2009) have also reported a positive correlation between the TSH and erythrocyte count. It has also been concluded that subclinical hypothyroidism occurs in patients with iron deficiency anemia (IDA) and is reversible with iron supplements to eradicate the dual disorder. At the end, it is interesting to note that nutritional deficiency, anemia, and hypothyroidism are all interlinked one with another. The parameters analyzed are in line with the deficiencies and morphological clinical manifestation linked to hypothyroidism.

Conclusion

In the present study, anemia was found as a common manifestation in hypothyroid individuals. Hypothyroidism is prevalent mainly in the female population, which is consistent with earlier literature data. The twin condition can cause significant

deterioration of the life quality when associated with fatigue and concomitant depression. Finally, anemia is not only caused due to deficiency of RBC, but other underlying causes like hypothyroidism that aid in a hematopoietic imbalance. Diagnosis of proper nutrient supplementation and hormonal treatment (levothyroxine) can help resolve both conditions.

Conflict of interest: *The authors declare no conflict of interest.*

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